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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/799,238 | 03/12/2004 | Elliott Richelson | 07039-126002 | 7520 |

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| EXAMINER | |
|---|---|
| EPPS FORD, JANET L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |

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| 05/15/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/799,238 | RICHELSON ET AL. | |
| | Examiner | Art Unit | |
| | Janet L. Epps-Ford | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Arguments*

1. The rejection of claims 15-26 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, and 21-25 of U.S. Patent No. 6,743,627 B1, is withdrawn in response to Applicant's filing of a terminal disclaimer filed 2-27-07.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 15-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the NTRA-PNA oligomer to "engender a biological response" in a rat challenged with neurotensin, and for reducing the expression of a target nucleic acid comprising the delivery of a polyamide nucleic acid oligomer comprising a neutral amide backbone, and comprising a sequence complementary to said target nucleic acid, does not reasonably provide enablement for the amelioration of any and all disease conditions in any mammal comprising the delivery of polyamide nucleic acid oligomer comprising a single neutral amide backbone linkage, and having a sequence complementary to a target nucleic acid, wherein the overexpression of said target nucleic acid is associated with said disease condition. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The scope of the instant claims encompass methods of *in vivo* delivery of polyamide nucleic acid oligomers comprising ***a neutral amide backbone linkage***, and a sequence that is complementary to a target nucleic acid sequence that is associated

with the production of a biological response. The scope of the phrase ***a neutral amide backbone linkage*** suggests that the PNA oligomers of the invention could encompass only a single neutral amide linkage in the backbone of the PNA structure, and may further comprise other backbone linkages that may render the PNA ionic or cationic, i.e. other than neutral. Moreover, the scope of the instant claims, therefore encompasses wherein the "[P]NA oligomers can be either modified or unmodified with the condition that they cross a biological barrier and engender a sequence specific biological response. Possible types of modification can include, but are not limited to, modifications with acridine, protein, backbone chemistries, DNA, peptide, bis-PNA, biotin, and fluorescein. Unmodified PNA oligomers can include any oligomer made essentially from PNA monomers, but without further modifications designed to enhance the crossing of plasma membranes or the BBB. Such unmodified PNA oligomers are designated herein as "carrier-free." It is to be understood, however, that "carrier-free" PNA oligomers can be modified in other ways, for example to enhance detectability (e.g., with various labels)." (see page 16, lines 8-16).

Moreover the scope of the claimed invention encompasses wherein the delivery of the polyamide nucleic acid oligomers comprising "a neutral polyamide backbone linkage," and "provides for the treatment of cells *in vivo* such that a behavioral response is observed in an organism," and further is "beneficial to gene therapy approaches involving the treatment of cancer, aging, behavioral diseases, infections, and auto-immune diseases." (see page 4 1$^{st}$ paragraph).

Additionally, Applicants suggest that the methods of the present invention can be used to treat a multitude of diseases, including those in brain, previously thought to be untreatable (e.g., Huntington's disease and Alzheimer's disease). (See page 27, 1st paragraph).

The specification as filed provides sufficient guidance for using the NTR1-PNA or AS-NTR1-PNA (SEQ ID NO: 1) to engender a biological response after intracranial or extracranial administration in a rat model system. However, with the exception of the nucleotide sequence of the polyamide used in the examples of the instant invention, the overall structure of the polyamide backbone is unclear. It is assumed that the PNA oligomers used in these examples comprised wherein the entire backbone of the oligomer comprised only neutral amide backbone linkages, based upon Applicant's description of PNA oligomers on page 1, paragraph #2 of the specification as filed. However, there are no examples set forth in the specification as filed that provide sufficient guidance for producing a biological response in a cell treated with a PNA oligomer comprising a single neutral amide backbone linkage.

The instant claims make no reference to a requirement that the polyamide structure of the PNA comprise wherein all of the linkages are neutral amide linkages. However, the nature of the polyamide structure appears to be critical to the hybridization properties of the PNA structure overall. See for example Buchardt et al. (US Patent 5,786,461), which states that replacing glycine in the backbone of a PNA by other amino acids result in a moderate loss in hybridization potency. Furthermore, the introduction of a negatively-charged side chain in the PNA backbone (e.g. glutamic acid

and aspartic acid) decreases hybridization potency as indicated by a decreased melting temperature (col. 63, lines 1-40).

According to Tyler '98 (Febs Let. Vol. 421, pp. 280-284; PTO-1449-DK) : "In vitro antisense studies targeting a variety of mRNA and DNA sequences have suggested that PNAs are potent inhibitors of protein production. This mechanism, while not completely understood, seems to be dependent on the base content of the PNA.." Additionally, Tyler et al. teach that although PNA oligomers possess superior properties over conventional antisense, PNA oligomers pass poorly into cells. Furthermore, although researchers have made derivative forms of PNAs to enhance transport into cells, there is no information whether these altered PNAs are able to inhibit protein expression. Therefore, cellular uptake of PNA oligomers is variable depending on the modification of PNA, as stated previously concerning antisense compounds. Moreover, Tyler et al. admits in their concluding remarks that "[f]urther experiments must be done in order to gain a fuller understanding of how PNAs are blocking protein expression and what happens to the PNAs within the animal and within the cell." Furthermore, Tyler et al. states that "applicability {of PNAs} to other types of proteins has yet to be examined," this statement suggests that the observations of Tyler et al. were not readily applicable to the delivery of all PNA oligomers for regulating the expression of all target genes.

Koppelhus et al. (2002) et al., page 52, 2nd paragraph, teach: A major obstacle for in vivo and ex vivo studies of the potential of PNA as antisense agent is the limited membrane permeability...and several methods have been applied to overcome the problem of delivery. Among these is the conjugation of PNA to certain "Trojan peptides"

reported to have a general cell membrane-penetrating capacity, making them capable of transporting a conjugated cargo to the interior of the cells." Moreover, on page 61, 2nd paragraph, Koppelhus et al. observed that "[O]ur results clearly demonstrate that uptake of PNA can be achieved in most of the tested cell types by conjugation to the peptides. However, the results also show that most of the PNA ends up in vesicular compartments of the cells. Therefore, the internalized PNA is not evenly distributed in the cytoplasm, and it is not significantly present in the nucleus. Thus, the major fraction of PNA is not present in the cellular compartments where it is supposed to exert its function as antisense agent." However, only a small amount of "the PNA escapes endocytotic entrapment and, thus, is able to act as an antisense agent.....Only carefully performed antisense experiments controlling for a specific effect on gene expression, including proper mismatch or genetic controls, will be able to conclusively demonstrate that this is the case. A comprehensive study being carried out in our laboratory is aimed at answering this question."

According to Rasmussen et al. (2006), several delivery protocols have been devised to overcome the poor cellular uptake of unmodified PNA. In regards to the various published studies of PNA in cellular systems, Rasmussen et al. stated (see page 44, 2nd paragraph): "To date, the published studies of PNA in cellular systems often represent isolated efforts in which a certain delivery protocol has been used in a single cell type during the investigation of a given gene by a specific methodology. The diversity in cell type, application, and methodology in these papers makes it virtually impossible to make reliable assessments about the relative efficiency of the different protocols." Moreover, Rasmussen et al. compared the efficacy of different transfection protocols. The study concluded with the following paragraph (see page 56):

"A final and important lesson from the present study was the finding that because of uncontrollable biologic factors, the absolute optimal transfection conditions will vary from experiment to experiment. Thus, to achieve really optimal cellular delivery of PNA in a specific experiment, these variations should be taken into account. This means that even though an optimized transfection protocol has been established, each experiment should include a systematic variation (around the optimal values) of critical transfection parameters, such as the concentration of PNA or the transfection reagent."

It is noted that the instant specification was filed on 3/12/04, however it claims priority back to 10/17/1997. As per MPEP § 2164.05(a) [R-2] "[W]hether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains.

The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b). The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

In the instant case, based upon the disclosures of Tyler et al. (1998), Koppelhus et al. (2002) and Rasmussen et al. (2006), it is clear that even today there is a significant level of unpredictability associated with the *in vivo* efficacy of PNA oligomers, particularly in regards to the variation in behavior of the oligomer as it relates to different cell types and methodology. Therefore, since the state of the art in regards to the use of PNA oligomers in antisense or antigene therapy remains unpredictable (as evidenced by the above references) it is concluded that the skilled artisan would have had to resort to undue experimentation to practice the full scope of the claimed invention due to significant breadth of the claims, the known unpredictability associated with the cellular uptake of PNA oligomers into cells, and the known variability associated with PNA behavior in different cells types, and the limited guidance provided in the specification as filed.

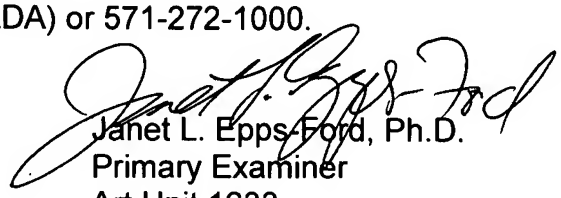
It is noted that Applicant's have filed multiple declarations under 37 CFR 1.132 during the prosecution of parent Applications 09/168,791, 08/953,269, and 09/016,685, to address the issue of enablement in these applications. However, it is noted that as per MPEP form paragraph 2.03: " Affidavits or declarations, such as those submitted

under 37 CFR 1.130, 1.131 and 1.132, filed during the prosecution of the prior application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit or declaration, the applicant should make the remarks of record in this application and include a copy of the original affidavit or declaration filed in the prior application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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Primary Examiner
Art Unit 1633

*JLE*